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NEW AGENTS TO PREVENT STROKES IN NONVALVULAR ATRIAL FIBRILLATION

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Introduction

Anticoagulation for atrial fibrillation has been dependant on warfarin for the past 30 years. However, the recent FDA approvals of dabigatran and rivaroxaban and the expected approval for apixaban have provided several new alternatives for our patients. Many factors must be considered when selecting the most appropriate agent for preventing stroke in nonvalvular atrial fibrillation. The following trials have provided the foundation for decision making when considering alternatives to warfarin therapy.

Pivotal Trials

Dabigatran

The RE-LY trial compared two doses of dabigatran (110 mg twice daily and 150 mg twice daily) against dose-adjusted warfarin.[1] The 150-mg dose of dabigatran proved superior to warfarin for stroke and systemic embolization (1.11% per year vs. 1.71% per year, P <0.001), whereas the 110-mg dose was noninferior (1.54% per year vs. 1.71% per year, P <0.001).[2] Major bleeding was similar with the 150-mg dose of dabigatran compared to warfarin (3.32% per year vs. 3.57% per year, P = 0.32); however, the 110-mg dose of dabigatran had significantly less bleeding complications (2.87% per year vs. 3.57% per year, P = 0.003).[2] Despite these outcomes, the FDA approved the 150-mg dose of dabigatran and the comparable 75-mg dose of dabigatran from pharmacokinetic models for patients with impaired renal function (creatinine clearance, or CrCl, between 15–30 mL/min).[3]

Rivaroxaban

The ROCKET-AF trial compared rivaroxaban 20 mg daily (or 15 mg daily for renal impairment) to dose-adjusted warfarin. Rivaroxaban was noninferior to warfarin for stroke and systemic emboli (1.7% per year vs. 2.2% per year, P <0.001).[4] The safety endpoint of major and nonmajor clinically relevant bleeding was similar between the two groups (14.9% per year vs. 14.5% per year, P = 0.44). The FDA approved the 20-mg daily dose for patients with a CrCl greater than 50 mL/min and a 15-mg daily dose for patients with a CrCl between 15–50 mL/min.[5]

Apixaban

Apixaban was studied in two atrial fibrillation trials: AVEROES and ARISTOTLE, both at 5 mg twice daily and 2.5 mg twice daily for patients at high risk of bleeding. In AVEROES, apixaban proved to be superior to aspirin monotherapy in reducing stroke and systemic embolism (1.6% per year vs. 3.7% per year, P <0.001). Major bleeding was similar between the two groups (1.4% per year vs. 1.2% per year, respectively; P = 0.57).[6] In ARISTOTLE, apixaban was proven superior to warfarin for stroke and systemic embolism (1.27% per year vs. 1.6% per year, P = 0.01). Significant reductions in major bleeding was also seen in apixaban patients (2.13% per year vs. 3.09% per year, P = 0.047).[7] The cardiorenal advisory committee for the FDA is to meet during the summer of 2012 to make recommendations for apixaban's application.

Clinical Considerations in Drug Use

Renal Function

Careful attention to renal function is necessary when considering any of the three new agents. All require dose reductions for impaired renal function and avoidance in end-stage renal disease and dialysis patients, whereas no such restrictions apply to warfarin. The minimum renal function, measured by CrCl, at enrollment in RE-LY and ROCKET-AF was 30 mL/min. However, the approved dosing for dabigatran allows a reduced dose for CrCl as low as 15 mL/min despite not having clinical outcomes from a randomized controlled trial.[1, 3, 4] The ARISTOTLE trial allowed a serum creatinine level up to 2.5 mg/dL or a CrCl >25 mL/min for inclusion into the trial and reduced the dose to 2.5 mg daily when two of following criteria were met: age ≥80 years, weight <60 kg, or serum creatinine ≥1.5 mg/dL.[7]

Drug Interactions

Drug interactions have plagued the patient on warfarin therapy. Currently, all oral anticoagulants have drug interactions with commonly used medications for rhythm or rate control of atrial fibrillation, although dose reductions for most of these drug interactions are not recommended with the new agents. Dabigatran is metabolized by ester hydrolysis with minimal conjugation and bypasses the Cytochrome P-450 (CYP-450) system. It does compete with P-glycoprotein pathways, and therefore a dose reduction is recommended for patients with a CrCl between 30–50 mL/min who are also taking dronedarone.[3] Rivaroxaban and apixaban both are metabolized through the CYP-450 system. Specifically, rivaroxaban is metabolized by CYP 3A4, 3A5, and 2J2, and apixaban is metabolized by 3A4 and 3A5.[5, 8] Specific dosing recommendations concerning drug interactions is minimal, and the current recommendation is to avoid concomitant therapy with metabolic inhibitors when possible due to increased risk for bleeding.[5] There are no practical/proven anticoagulation assays to help direct dosage adjustment for any of the newer anticoagulants to account for these interactions. The ability to monitor the international normalized ratio (INR) to a goal of 2 to 3 is a perceived advantage of warfarin.

Anticoagulation Management

In contrast, an advantage of the newer agents over warfarin is the rapid onset of anticoagulation and sustained durability. This is particularly advantageous during the cardioversion of

atrial fibrillation. Unless closely monitored, the unpredictability and delay of warfarin's anticoagulation effect may lead to subtherapeutic or supratherapeutic levels, causing delays in procedures and increasing the patient's risks. Newer agents provide prompt anticoagulation effects with the first dose.[3, 5]

The ability to reverse warfarin with proven strategies including fresh frozen plasma and vitamin K is an advantage. Dabigatran, rivaroxaban, and apixaban do not have specific reversal strategies confirmed in clinical practice. Presently, there is some literature suggesting that fresh frozen plasma or prothrombin complex concentrates are potential treatments. However, this data has not been established.[9, 10]

Even in the best of hands, maintenance of INRs between 2 to 3 while on warfarin ranges from 44–77%.[1, 2,4, 7, 11] A subtherapeutic level may be associated with an increased stroke risk and a supratherapeutic level with an increased risk of bleeding. This fact is probably why two of the three newer agents have proven superiority over warfarin. However, warfarin patients who have a history of high compliance and are consistently maintained appropriately may not benefit from switching to a newer agent.[11]

Conclusion

To date, we have three new choices for oral anticoagulation to help prevent stroke in patients with nonvalvular atrial fibrillation. Warfarin, the veteran anticoagulant with known interactions, monitoring, and reversibility, still remains a viable option for treatment, especially in well-controlled patients. Dabigatran is the only available agent with established superiority in preventing stroke. Rivaroxaban a noninferior choice compared to warfarin with once-daily dosing. Apixaban awaits FDA review and probable approval and is the only agent with superior efficacy and safety. Our views of the advantages and disadvantages of each agent are summarized in Table 1.

Table 1. Advantages and disadvantages of stroke-prevention agents for nonvalvular atrial fibrillation.

Agent	Clinical Advantages	Disadvantages
Warfarin	• Dosed independent of renal function • Can be monitored • Established reversal strategies • Inexpensive drug cost • Valvular disease management with established guidelines • 30-year familiarity • Concomitant aspirin and clopidogrel data available • Can be crushed	• Even in expert hands, 30%–50% of time INR is out of recommended range (2–3) • CYP-450 interactions • Multiple dosing changes • Requires days to achieve complete anticoagulation • Inferior to dabigatran (stroke and embolism) and apixaban (stroke, embolism, and bleeding)
Dabigatran	• The only FDA-approved superior agent to warfarin for stroke prevention • Fast onset of anticoagulation (within 3 hours) • No CYP-450 interactions	• One proven dose (150 mg BID) and one pharmacokinetic model (75 mg BID) • 110-mg dose not approved in U.S.A. • No established monitoring strategy • No established reversal strategy • Increased GI bleeding • Drug cost • Cannot be crushed; must be taken as whole capsule • Renal adjustment for impairment and avoidance in end-stage renal disease
Rivaroxaban	• Two doses approved with clinical database support • Fast onset of anticoagulation (within 3 hours) • Can be crushed and administered • Approved for once-daily dosing	• Not superior to warfarin for stroke prevention • No established monitoring strategy • No established reversal strategy • Increased GI bleeding • CYP-450 interactions • Drug cost • Renal adjustment for impairment and avoidance in end-stage renal disease
Apixaban (awaiting FDA approval)	• Superior efficacy and safety compared to warfarin • Fast onset of anticoagulation (within 3 hours) • Two independent trials in atrial fibrillation (apixaban vs. warfarin & apixaban vs. aspirin)	• Not yet available (FDA advisory board to meet in late summer) • Multi-stepped dose reduction for high-risk patients • No established monitoring strategy • No established reversal strategy • CYP-450 interactions • Drug cost • Renal adjustment for impairment and avoidance in end-stage renal disease

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References

1. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51.
2. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al.; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51.
3. Pradaxa [package insert]. Ridgefield (CT): Boehringer Ingelheim Pharmaceuticals, Inc.; 2012.
4. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011 Sep 8;365(10):883-91.
5. Xarelto [package insert]. Titusville (NJ): Janssen Pharmaceuticals, Inc.; 2011.
6. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsen S, et al. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011 Mar 3;364(9):806-17.
7. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011 Sep 15;365(11):981-92.
8. Micromedex Gateway [Internet]. New York (NY): Thomson Reuters Healthcare; 2012 Apr 10 [cited 2012 Jul 13]. Available from: http://www.thomsonhc.com.
9. Kaatz S, Kouides PA, Garcia DA, Spyropolous AC, Crowther M, Couketis JD, et al. Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. Am. J Hematol. 2012 May;87 Suppl 1:S1141-5.
10. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation. 2011 Oct 4;124(14):1573-9.
11. Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet. 2010 Sep 18;376(9745):975-83.